

Ultrafine and Fine Particle Number and Surface Area Concentrations and Daily Cause-Specific Mortality in the Ruhr Area, Germany, 2009–2014

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BACKGROUND: Although epidemiologic studies have shown associations between particle mass and daily mortality, evidence on other particle metrics is weak.

OBJECTIVES: We investigated associations of size-specific particle number concentration (PNC) and lung-deposited particle surface area concentration (PSC) with cause-specific daily mortality in contrast to PM₁₀.

METHODS: We used time-series data (March 2009–December 2014) on daily natural, cardiovascular, and respiratory mortality (NM, CVM, RM) of three adjacent cities in the Ruhr Area, Germany. Size-specific PNC (electric mobility diameter of 13.3–750 nm), PSC, and PM₁₀ were measured at an urban background monitoring site. In single- and multipollutant Poisson regression models, we estimated percentage change (95% confidence interval) [% (95% CI)] in mortality per interquartile range (IQR) in exposure at single-day (0–7) and aggregated lags (0–1, 2–3, 4–7), accounting for time trend, temperature, humidity, day of week, holidays, period of seasonal population decrease, and influenza.

RESULTS: PNC_{100–750} and PSC were highly correlated and had similar immediate (lag0–1) and delayed (lag4–7) associations with NM and CVM, for example, 1.12% (95% CI: 0.09, 2.33) and 1.56% (95% CI: 0.22, 2.92) higher NM with IQR increases in PNC_{100–750} at lag0–1 and lag4–7, respectively, which were slightly stronger than associations with IQR increases in PM₁₀. Positive associations between PNC and NM were strongest for accumulation mode particles (PNC 100–500 nm), and for larger UFPs (PNC 50–100 nm). Associations between NM and PNC_{<100} changed little after adjustment for O₃ or PM₁₀, but were more sensitive to adjustment for NO₂.

CONCLUSION: Size-specific PNC (50–500 nm) and lung-deposited PSC were associated with natural and cardiovascular mortality in the Ruhr Area. Although associations were similar to those estimated for an IQR increase in PM₁₀, particle number size distributions can be linked to emission sources, and thus may be more informative for potential public health interventions. Moreover, PSC could be used as an alternative metric that integrates particle size distribution as well as deposition efficiency. <https://doi.org/10.1289/EHP2054>

Introduction

Increases of daily fine particulate matter [PM ≤ 2.5 μm and ≤ 10 μm , respectively, in aerodynamic diameter (PM_{2.5} and PM₁₀)] have been shown to be associated with natural mortality (NM) in several North American and European cities (HEI 2010; Katsouyanni and Samet 2009; Samoli et al. 2008). Epidemiological studies have further shown that PM is associated with adverse health effects, such as short- and long-term cardiovascular morbidity and mortality, diseases of the central nervous system, respiratory morbidity, and lung cancer (WHO 2013). Toxicological studies suggest that inhaled ultrafine particles (UFPs) might be particularly harmful, because they can pass the lung epithelium more easily and translocate into the blood to be transported to other organs (Oberdörster et al. 2005). However, epidemiological evidence on pathogenic health effects of UFPs is still limited and inconclusive (HEI Review Panel on Ultrafine Particles 2013; WHO 2013), mainly due to the

lack of routinely monitored UFP data and few dedicated measurement campaigns in the framework of specific research projects. UFPs are commonly measured as particle number concentration (PNC), representing more than 85% of the total PM_{2.5} particle number (Hinds 1999) while contributing little to the PM concentration. The latter is usually the only regulated ambient air particle metric worldwide. Although PM is a mixture composed by different particle sizes and numbers, particles of different size and number concentration are usually generated by different sources (Morawska et al. 1999) such that size and number distribution may provide a better understanding to identify sources as a potential basis for an intervention measure. The commonly used UFPs, defined as particles with an electric diameter < 100 nm, for example, combine nucleation and Aitken mode particles (< 30 nm and 30–100 nm respectively), whereas combustion-generated particles (from vehicle emissions) range from 30 nm to 500 nm (Vu et al. 2015). UFP concentration alone therefore does not inform about the different sources of the particles.

Another potentially important metric is the integrated measure of lung-deposited surface area concentration of airborne particles (PSC), which takes into account the surface area as well as the size-dependent deposition efficiency of respective particles in the respiratory system. This metric thus constitutes a proxy of the particle's reactivity, which is related to surface area, as well as its capacity to carry adsorbed chemical species, both possibly promoting oxidative stress, a precursor of inflammatory effects (Hussain et al. 2009). Besides PM, PNC in different size fractions and particle surface area may hence provide a better measurement regarding the toxicity of PM exposure (Noël et al. 2016; Oberdörster 2000) as well as the identification of sources (Morawska et al. 1999).

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In a European multicenter analysis on health effects of UFP number on natural and cardiorespiratory mortality including Finland, Sweden, Denmark, Germany, Italy, Spain, and Greece (Stafoggia et al. 2017), a weak delayed effect of UFP was estimated ($>lag5$). However, this multicenter study was limited by the heterogeneity of its exposure assessment methodology such as instrumentation capturing slightly different size ranges of particles or placement of monitors (background vs. traffic location) as well as by different measurement periods (time and duration) (Stafoggia et al. 2017). A slight difference in the size ranges of measured UFPs due to the use of different instruments has a great impact on the measured overall PNC because the number concentration of particles increases remarkably in the smallest size fractions. Moreover, the location of the monitoring equipment (height and placement of monitors with respect to local sources and the location of the study population) also substantially influence the representativeness of the exposure measurements and might introduce bias as a consequence of differential exposure measurement error (Stafoggia et al. 2017).

In this study we tried to overcome the aforementioned limitations by focusing on one large single study, located in the densely populated German Ruhr Area (Essen, Mülheim, and Oberhausen). Being part of the German Ultrafine Aerosol Network (GUAN) (Birmili et al. 2016), this time-series study benefits from a comparatively long measurement period of almost 6 y and an in-depth characterization of ultrafine (electric mobility diameter <100 nm, including the size ranges 13.3–30, 30–50, and 50–100 nm) and fine (electric mobility diameter 100–750 nm, including the size ranges 100–250, 250–500, and 500–750 nm) particles, including number concentration and lung-deposited PSC, a metric that has rarely been investigated in epidemiological studies to date. In addition, the measurement site is co-located with a central urban background monitoring station of the regional air quality network (Mülheim Styrum), enabling us to also make use of monitored PM_{10} , nitrogen dioxide (NO_2), and ozone (O_3), which potentially confound or modify ultrafine or fine particle effects on health. In a recent meta-analysis, NO_2 and $PM_{2.5}$ both were associated with mortality in multipollutant analyses (Faustini et al. 2014), whereas O_3 is highly correlated with temperature and sunlight, and hence might be an additional or even independent risk factor (Levy et al. 2012). Considering that multiple air pollutants originate from common sources, multiple air pollutants may interact with or confound each other. Results of the European study indicated that associations between UFPs and mortality were confounded by NO_2 , $PM_{2.5}$, and $PM_{2.5-10}$; whereas adjusting for PM_{10} or O_3 had little influence on effect estimates (Stafoggia et al. 2017).

The objective of this study was to investigate the associations of size-specific PNC as well as lung-deposited PSC on natural, cardiovascular, and respiratory mortality in the Ruhr Area, based on a time-series study from March 2009 to December 2014. In addition to the toxicologically important novel particle metrics, we investigated the role of copollutants such as PM_{10} , NO_2 , and O_3 .

Methods

Mortality Data

We collected daily mortality counts based on the primary cause of death, defined as natural [International Classification of Diseases, 10th Revision (ICD-10) A00–R99], cardiovascular (ICD-10 I00–I99) and respiratory (ICD-10 J00–J99) mortality in the three adjacent cities of Essen, Mülheim, and Oberhausen between January 2008 and December 2014 from the central statistical and IT services provider of North Rhine-Westphalia. The three adjacent cities (in an area of ~ 379 km²) with a total of nearly

1 million inhabitants [Essen, $\sim 580,000$ (210 km²); Mülheim, $\sim 170,000$ (91 km²); and Oberhausen, $\sim 211,000$ (77 km²)] are located in the western part of the metropolitan Ruhr Area. As respective outcomes, we used the sum of city-specific natural and cause-specific deaths per day. The primary cause of deaths was assigned based on the underlying disease instead of the immediate cause of death.

Air Pollution Data

Exposure data was collected at the project-specific measurement site (i.e., GUAN) provided by the Institute of Energy and Environmental Technology (IUTA), co-located to an urban background monitoring site of the regional air quality network (code “STYR”) operated by the North Rhine-Westphalia State Agency for Nature, Environment and Consumer Protection [Landesamt für Natur, Umwelt und Verbraucherschutz (LANUV) North Rhine-Westphalia (NRW), Essen, Germany] from March 2009 until December 2014. A detailed description of the measurement site and respective measurement techniques can be found elsewhere (Birmili et al. 2016). The measurement site is located close to the administrative border of the cities of Mülheim and Oberhausen. Within a 1-km buffer, the site is surrounded by highways with channel-like cross-sections (~ 10 m below site level) and traffic of approximately 50,000 vehicles/day (~ 250 m north), a railway yard (south/southwest), and a medium-trafficked street and its junction with a highway exit (west/northwest). Main wind directions are south/southwest and northeast. The mixed residential-, industrial-, and traffic-influenced character of the site is typical for many urban areas in the Ruhr Area and hence believed to be representative for a large part of the population living in the adjacent cities of Mülheim and Oberhausen, including their eastern neighbor Essen.

Measured particle characteristics included size-specific PNC of ultrafine, fine, and coarse particles (as well as their PSC) that deposit in the alveolar or tracheobronchial region of the lung (short: lung-deposited PSC). PNCs [number per cubic centimeter (n/cm^3)] were measured with a scanning mobility particle sizer (TSI Inc.) in the size ranges of 13.3–750 nm electrical mobility diameter (Wang and Flagan 1990). In an effort to understand the health effects of different particle sizes, potentially generated by different emission sources and reaction processes, we investigated six particle size fractions, including particles size ranges of 13.3–30 nm (reflecting the nucleation mode: <30 nm), 30–50 nm, 50–100 nm (reflecting the Aitken mode: 30–100 nm), 100–250 nm, 250–500 nm, and 500–750 nm (reflecting the accumulation mode: 100–1,000 nm). The PSC of lung-deposited particles with a diameter of 20–1,000 nm was measured in micrometers squared per cubic centimeter every second using a nanoparticle surface area monitor (NSAM; model 3550, TSI Inc.) (Asbach et al. 2009). The NSAM uses an opposed flow unipolar diffusion charger followed by an ion trap to remove excess ions. Particles >1 μ m are withheld by means of an impactor located at the NSAM entrance. The voltage in the ion trap can be adjusted to manipulate the particle size distribution and therefore the response function; that is, if the ion trap voltage is set to 200 V, the NSAM delivers the surface area deposited in the alveolar region, whereas it delivers the surface area of particles deposited in the tracheobronchial region when the voltage is set to 100 V. In our study, alveolar-deposited particles were monitored. The accuracy of surface determination decreases substantially for particle diameters below 20 nm and above 400 nm (Asbach et al. 2009). However, typical outdoor aerosol particles <20 nm in diameter and >400 nm in aerodynamic diameter contribute little to the total surface area.

Routinely monitored air pollutants at the central state-run (LANUV) monitoring site (STYR) included PM_{10} (β -attenuation), NO_2 (chemiluminescence method), and O_3 (ultraviolet absorption).

Covariates

Daily temperature [in degrees Celsius (°C), daily mean] and relative humidity were measured according to standardized protocols (VDI-guidelines 3786, parts 3 and 4; Verein Deutscher Ingenieure 2009, 2012) at a state-run monitoring site (Duisburg-Walsum), located 11 km northeasterly from the study site. External information on periods of influenza was collected from the central statistical and information technology services provider of North Rhine-Westphalia. In addition, we defined an indicator for population decrease during summer, following the definition in Stafoggia et al. (2017): namely a three-level variable assuming value “1” for the time of school holidays in North Rhine-Westphalia (6 wk within July and September; e.g., 9 July until 21 August in 2012 or 22 July until 3 September in 2013), and “2” in the 4-wk period around the school holidays; all other days stood for reference days and were assigned to “0”). Further variables included day of week (six indicator variables, with Sundays as the reference category), holiday (an indicator variable identifying the main bank holidays in North Rhine-Westphalia), and season (fall = September–November; spring = March–May, summer = June–August; and winter = December–February).

Statistical Analysis

The basic description of particle metrics, mortality, and meteorological data included visualizations of the time series, median [interquartile range (IQR)], and Spearman's correlation coefficients between respective exposure variables.

To estimate associations between exposures and daily cause-specific mortality, we used Poisson regression models allowing for overdispersion. Regression models included penalized regression splines as a smoothing function for time trend. We further included potential confounders based on a review of current literature (Stafoggia et al. 2017). Adjusted models included mean air temperature [day of death (lag0) and a moving average of 1–3 d prior to the observed death (lag1–3)], relative humidity, and indicator variables for day of the week, holidays, influenza epidemics, and the presence of a population decrease in the respective cities during the summer vacation period. Air temperature was modeled by fitting a natural cubic regression spline to allow for nonlinear confounder adjustment.

We investigated single-lags from the same day of death (lag0) up to 7 d prior to death (lag7). Moreover, we investigated aggregated lags, representing immediate effects (0–1 d prior to the death; lag0–1), medium-term effects (lag2–3), and delayed effects (lag4–7). We chose single-lag models as well as aggregated 2- to 4-d lags over distributed lag-models because of multiple missing data in the PNC series and the respective loss of power, especially in the underlying small study population. By ending up with 11 models per investigated pollutant, we aimed to look for a general pattern of associations rather than identifying adverse health effects based on single-day lags that could be observed in such a multiple testing situation.

The main exposure metrics of interest were size-specific PNC, aggregated as ultrafine (PNC_{<100}) and fine particles (PNC_{100–750}), as well as PSC and PM₁₀. In addition, we also investigated size-specific PNC in finer resolved size fractions (PNC_{13.3–30}, PNC_{30–50}, PNC_{50–100}, PNC_{100–250}, PNC_{250–500}, and PNC_{500–750}). All health effect estimates are presented as mean percentage increase [95% confidence interval (CI)] [% (95% CI)] in mortality per IQR of the respective exposure.

We calculated two-pollutant models in order to investigate whether results for UFPs (PNC_{<100}) were independent of other pollutants or metrics: a) PNC_{<100} and PM₁₀, b) PNC_{<100} and NO₂, c) PNC_{<100} and O₃, d) PNC_{<100} and PNC_{100–750}, and e) PNC_{<100} and PSC. In addition we investigated two-pollutant models

including a) PNC_{100–750} and PM₁₀, b) PNC_{100–750} and NO₂, c) PNC_{100–750} and O₃, and d) PNC_{100–750} and PSC.

Furthermore, we investigated effect modification of UFPs and particles (PNC_{100–750}) by cold and warm periods of the year (October–March vs. April–September), and by high or low concentration of PM₁₀, O₃, NO₂ and PSC by including interaction terms between the potential effect modifier and the exposure of interest. High levels of PM₁₀, O₃, NO₂, and PSC referred to concentrations above the 75th percentile of the respective distribution. Effect modification was checked based on a 5% significance level regarding the coefficient of the respective interaction term.

Results

Because particle metrics (PNC and PSC) were only measured beginning in March 2009, our analysis was based on the time period from March 2009 until December 2014 (2,132 d). We observed different missing patterns among exposures ranging from 266 missing days for PNC, 125 d for PSC, 110 d for O₃, and 91 d for NO₂ to 29 d for PM₁₀. The majority of missing exposure data for PNC resulted from a sampling pump failure of the scanning mobility particle sizer during specific time windows (data not shown) and hence was assumed to be missing at random. Because of different missing patterns, the number of observations slightly changed between the analysis for each metric and lag.

Medians (IQRs) of daily cause-specific mortality per approximately 946,000 inhabitants in Essen, Mülheim, and Oberhausen were 32 (8) death/day for natural, 12 (5) for cardiovascular (corresponding to 37.5% of the overall deaths), and 3 (2) for respiratory mortality (corresponding to 9.4% of the overall deaths) (Table 1 and Figure 1). The city of Essen contributed most to the observed mortality (approximately 60%). Median (IQR) PNC of UFPs (PNC_{<100}) was 9,871 n/cm³ (4,900), with the smallest size fraction (PNC_{13.3–30}) contributing the most to PNC (4,623 n/cm³; 2,438). Median PSC was 36.1 μm²/cm³ (21.7) and PM₁₀ was 20.2 μg/m³ (13.3), which is well below the European annual limit value of 40 μg/m³. In total, the PM₁₀ 24-h limit (50 μg/m³; EU 2008) was exceeded on 108 d (Figure 1). The median for

Table 1. Median (IQR) daily mortality, particle metrics, and meteorology in the Ruhr Area (Essen, Mülheim, and Oberhausen) between March 2009 and December 2014 (2,132 days).

Variable	Median (IQR)	Days (n) ^a
Mortality		
Natural ^b	32.0 (8.0)	2,132
Cardiovascular ^c	12.0 (5.0)	2,132
Respiratory ^d	3.0 (2.0)	2,132
Exposure PNC (n/cm ³)		
PNC _{13.3–30}	4,623.1 (2438.2)	1,866
PNC _{30–50}	2,673.1 (1492.5)	1,866
PNC _{50–100}	2,368.7 (1608.7)	1,866
PNC _{<100} (UFP)	9,870.6 (4900.2)	1,866
PNC _{100–250}	1,209.7 (903.2)	1,866
PNC _{250–500}	195.8 (180.8)	1,866
PNC _{500–750}	9.0 (14.0)	1,866
PNC _{100–750} (FP)	1,437.3 (1060.9)	1,866
PSC (μm ² /cm ³)	36.1 (21.7)	2,007
PM ₁₀ (μg/m ³)	20.2 (13.3)	2,103
NO ₂ (μg/m ³)	29.2 (16.2)	2,041
O ₃ (μg/m ³)	54.0 (37.0)	2,022
Meteorology		
Temperature (°C)	11.9 (9.9)	2,124
Relative humidity	78.8 (18.5)	2,124

^aThe number of days differs because of inconsistencies in measurements.

^bEssen: 19.0 (6.0); Oberhausen 7.0 (4.0); Mülheim: 5.0 (3.0).

^cEssen: 7.0 (4.0); Oberhausen 2.0 (3.0); Mülheim: 2.0 (2.0).

^dEssen: 2.0 (2.0); Oberhausen 0.0 (1.0); Mülheim: 0.0 (1.0).

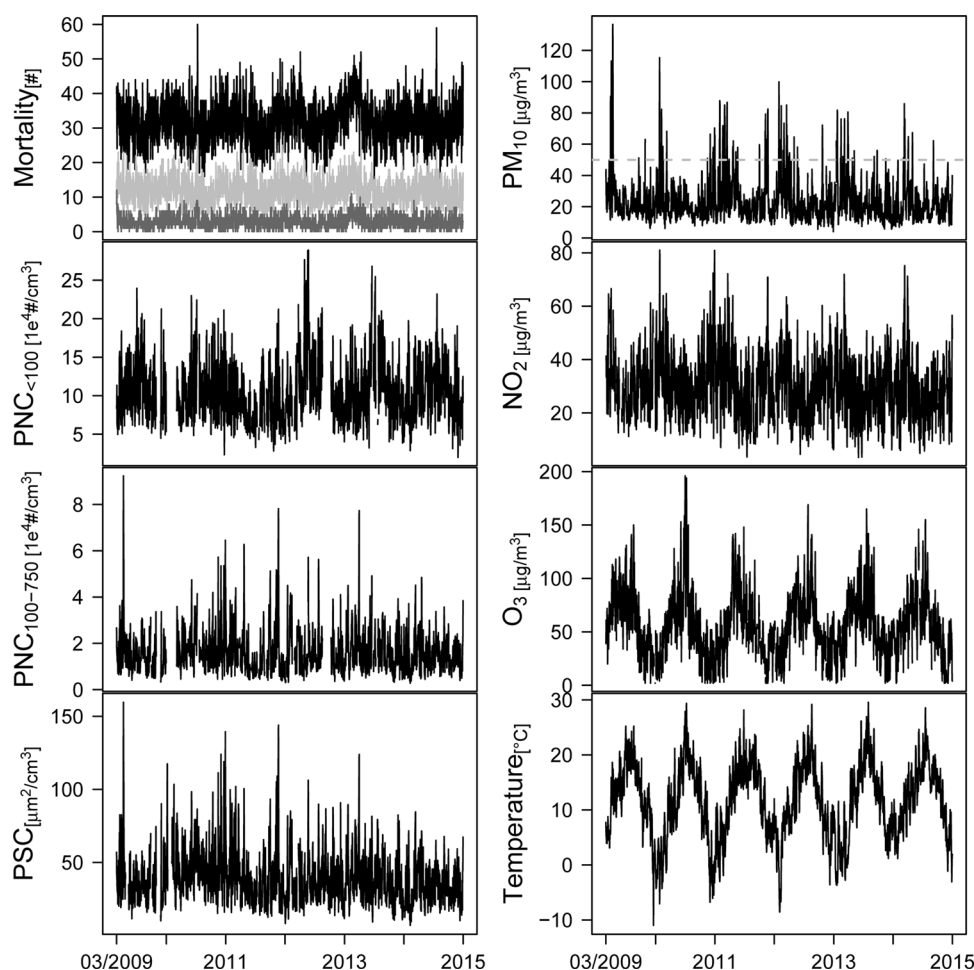


Figure 1. Time series of daily cause-specific mortality (top left panel: natural mortality is shown in black, cardiovascular mortality is shown in gray, and respiratory mortality is shown in dark gray), PNC_{<100}, PNC_{100–750}, PSC, PM₁₀ (top right panel: the dashed horizontal line indicates the 24-h limit of 50 µg/m³), NO₂, O₃, and temperature in the Ruhr Area. Note: NO₂, nitrogen dioxide; O₃, ozone; PM₁₀, particulate matter ≤ 10 µm in aerodynamic diameter; PNC_{<100}, size-specific particle number concentration of particles < 100 nm electrical mobility diameter; PNC_{100–750}, PNC of particles with 100–750 nm electrical mobility diameter; PSC, particle surface area concentration.

NO₂ was 29.2 µg/m³ (16.2), which was also below the annual limit value of 40 µg/m³. The median temperature was 11.9°C (9.9), and relative humidity 78.8% (18.5).

Spearman correlation (*r*) between air pollutants ranged from −0.39 (for NO₂ and O₃) to 0.99 (PNC_{100–250} and PNC_{100–750}) (Table 2; based on data for 1,669 d with complete measurement data for all exposure metrics and pollutants.). PNC_{<100} (UFPs) generally correlated moderately with PSC and NO₂ (*r* = 0.63

and *r* = 0.42), and correlated considerably more weakly with PM₁₀ and O₃ (*r* = 0.26 and *r* = 0.14). The smallest size fraction (PNC_{13.3–30}) correlated weakly with other particle metrics and pollutants (0.00 ≤ *r* ≤ 0.28). PNC_{100–750} revealed overall high correlations with the particle metrics PSC (*r* = 0.94) and PM₁₀ (*r* = 0.74). PNC_{100–750} correlated slightly weaker with NO₂ than PNC_{<100} (*r* = 0.65), whereas no correlation was observed between PNC_{100–750} and O₃.

Table 2. Correlation coefficients (Spearman *r*) between exposure metrics and pollutants (*n* = 1,669) in the Ruhr Area between March 2009 and December 2014 based on daily-based complete case data for all exposures, *n* = 1,669.

	PNC _{<100}	PNC _{100–750}	PNC _{13.3–30}	PNC _{30–50}	PNC _{50–100}	PNC _{100–250}	PNC _{250–500}	PNC _{500–750}	PSC	PM ₁₀	NO ₂
PNC _{<100}	1										
PNC _{100–750}	0.56	1									
PNC _{13.3–30}	0.86	0.25	1								
PNC _{30–50}	0.92	0.53	0.67	1							
PNC _{50–100}	0.79	0.85	0.43	0.82	1						
PNC _{100–250}	0.60	0.99	0.28	0.57	0.87	1					
PNC _{250–500}	0.27	0.82	0.03*	0.26	0.56	0.74	1				
PNC _{500–750}	0.21	0.71	−0.01*	0.21	0.49	0.64	0.9	1			
PSC	0.63	0.94	0.28	0.66	0.90	0.93	0.76	0.68	1		
PM ₁₀	0.26	0.74	0.00*	0.28	0.55	0.69	0.82	0.81	0.73	1	
NO ₂	0.42	0.65	0.22	0.41	0.57	0.63	0.59	0.58	0.70	0.63	1
O ₃	0.14	−0.01*	0.15	0.13	0.06	0.03*	−0.19	−0.25	−0.04*	−0.12	−0.39

**p* > 0.05, all other *p* ≤ 0.05.

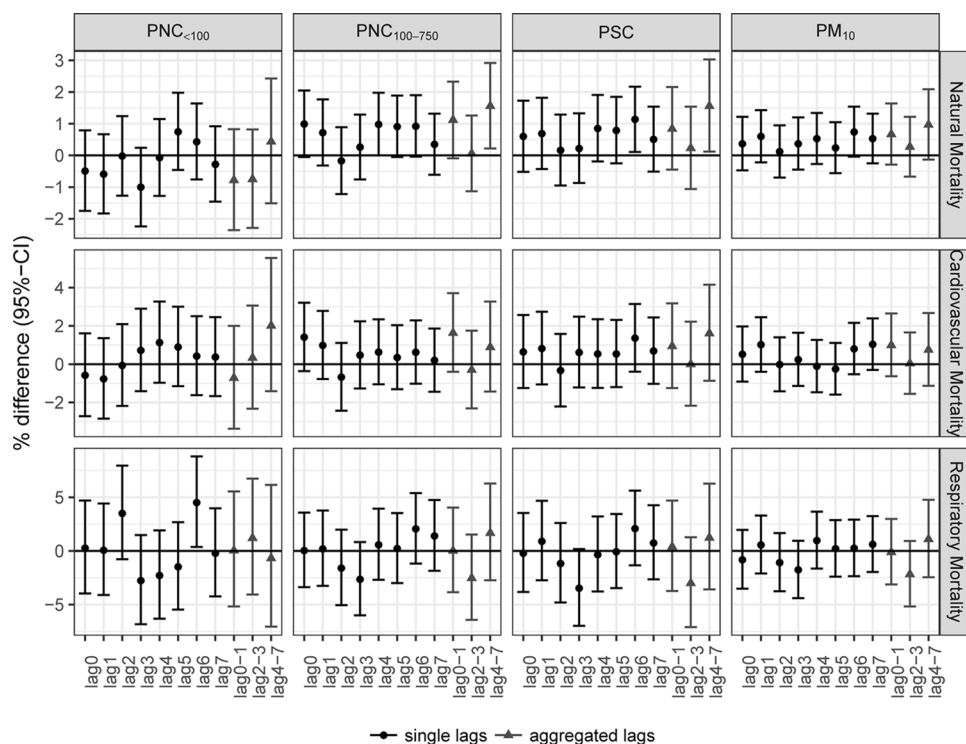


Figure 2. Short-term associations per IQR increase of air pollutant concentration and daily natural and cause-specific mortality in the Ruhr Area between March 2009 and December 2014, estimated for different particle metrics (PNC_{<100}, PNC_{100–750}, PSC, and PM₁₀) at single-day lags (lag0–lag7) and for aggregated lags (lag0–1, lag2–3, lag4–7) in Poisson regression models, adjusted for time trend, temperature, humidity, day of week, holidays, period of seasonal population decrease, and influenza. (Corresponding numeric data are provided in Table S1.) Note: IQR, interquartile range; NO₂, nitrogen dioxide; PM₁₀, particulate matter ≤10 μm in aerodynamic diameter; PNC_{<100}, size-specific particle number concentration of particles <100 nm electrical mobility diameter; PNC_{100–750}, PNC of particles with 100–750 nm electrical mobility diameter; PSC, particle surface area concentration.

Main Effects

Estimated associations of exposure with mortality showed different patterns for the different particle metrics and causes of mortality (Figure 2). Overall patterns of PNC_{100–750} and PSC were similar and comparable to those of PM₁₀, showing immediate (lag0–1) and delayed (lag4–7) associations for NM and cardiovascular mortality (CVM) (Figure 2). Point estimates for immediate associations (lag0–1) of PNC_{100–750} were 1.12% (95% CI: –0.09, 2.33) for NM and 1.63% (95% CI: –0.40, 3.71) for CVM (see Table S1), and for more delayed associations (lag4–7) 1.56% (95% CI: 0.22, 2.92) for NM and 0.89% (95% CI: –0.43, 3.27) for CVM (see Table S1). These effect estimates were slightly stronger than those of PM₁₀ on an IQR basis with an immediate (lag0–1) increase in NM and CVM of 0.67% (95% CI: –0.29, 1.64) and 0.99% (95% CI: –0.63, 2.65) or a more delayed (lag4–7) increase in NM and CVM of 0.97% (95% CI: –0.13, 2.09) and 0.75% (95% CI: –1.13, 2.67) (Figure 2; see also Table S1). We did not observe clear associations between PNC_{<100} (UFP) and NM or CVM, although the observed pattern suggested a more delayed association (lag4–7) with a slightly higher point estimate of 2.01% (95% CI: –1.41, 5.55), yet estimated less precisely (Figure 2; see also Table S1). For respiratory mortality (RM) we observed comparatively strong single-day associations at lag2 and lag6 with PNC_{<100} of 3.50% (95% CI: –0.77, 7.95) and 4.51% (95% CI: 0.37, 8.81), respectively. However, there were no conclusive patterns linking RM with aggregated lag-exposures of the considered pollutants.

When looking at size-specific associations in more detail (Figure 3; see also Table S2), we observed immediate inverse associations of PNC_{13.3–30} with NM and CVM (–1.81% (95% CI: –3.30, –0.30) and –1.63% (95% CI: –4.16, 0.97), respectively;

whereas for lag4–7, the estimate for NM moved close to the null and that for CVM was positive (95% CI: –0.55% (–2.40, 1.34) and 1.43% (95% CI: –1.86, 4.83) respectively). In contrast, patterns for PNC with an electric diameter >50–500 nm pointed to positive immediate (lag0–1) and delayed (lag4–7) associations with NM and CVM, similar to associations of PNC_{100–750}, PSC and PM₁₀. Clearest associations were observed for particles of 100–250 and 250–500 nm size and NM. For RM, patterns were less conclusive, yet somewhat different from NM and CVM, indicating only delayed associations with larger particles (electric diameter >250 nm).

Adjustment for Copollutants

Effect estimates for NM and CVM in association with PNC_{<100} and PNC_{100–750} were similar after adjustment for O₃ (Figure 4). In general, effect estimates were mostly robust towards adjustment for PM₁₀, though associations between lag 4–7 PNC_{<100} and NM became more negative. Adjustment for NO₂ on the other hand showed a slightly different pattern: Although effect estimates for UFP on CVM were unaffected by NO₂ adjustment, effect estimates for PNC_{<100} and NM became more negative over all considered lags. Effect estimates for PNC_{100–750} on both NM and CVM were essentially unchanged after NO₂ adjustment. After adjustment for PSC or PNC_{100–750}, associations for PNC_{<100} and NM or CVM were similar to those adjusted for NO₂. Associations between PNC_{100–750} and both outcomes at lag0–1 became more positive with adjustment for PSC, whereas the association between PNC_{100–750} and CVM at lag4–7 became negative, although confidence intervals were wide.

Associations between PNC_{13.3–30} and mortality remained unchanged after adjustment for other metrics (see Figure S1),

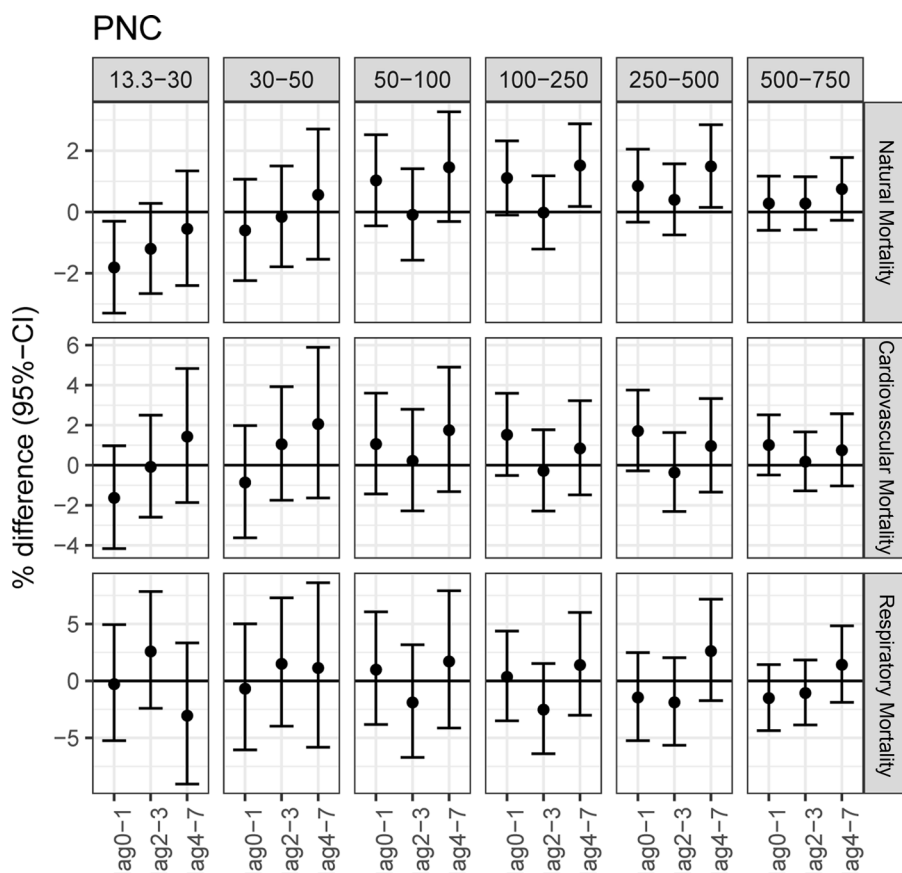


Figure 3. Short-term associations (lag0–1, lag2–3, lag4–7) per IQR increase of size-specific particle number concentrations and daily natural and cause-specific mortality in the Ruhr Area between March 2009 and December 2014, estimated in Poisson regression models, adjusted for time trend, temperature, humidity, day of week, holidays, period of seasonal population decrease, and influenza and presented as percentage differences (95% confidence interval) [% (95% CI)] in mortality. (Corresponding numeric data are provided in Table S2.) IQR, interquartile range.

consistent with expectations given the weak correlations with other pollutants (Table 2).

Effect Modification

Effect modification of associations between fine or ultrafine PNCs and natural or CV mortality were significant only for NM in association with O_3 and $PNC_{<100}$ at lag4–7 (interaction $p=0.03$), where $PNC_{<100}$ was positively associated with NM when O_3 was below the 75th percentile (1.31%; 95% CI: $-0.46, 3.11$), and negatively associated with NM when O_3 was high (-1.94% ; 95% CI: $-4.63, 0.83$) (Figure 5; see also Table S3). A similar pattern was observed for CVM in association with high or low O_3 and $PNC_{<100}$ at lag0–1 (interaction $p=0.03$). We did not observe significant (defined as interaction $p<0.05$) effect modification by season or higher levels of co-exposure (PM_{10} , NO_2 , or PSC) regarding associations between fine or ultrafine PNCs and NM or CVM. However, at lag4–7, point estimates for $PNC_{<100}$ were positive among those with lower levels of PM_{10} , NO_2 , and PSC, but closer to the null among those with higher levels of co-exposure (interaction p : 0.17–0.67). Similarly, for NM and CVM, associations with $PNC_{100-750}$ at lag0–1 were stronger for those with higher versus lower levels of PM_{10} , NO_2 , and PSC co-exposure (interaction $p=0.15$ –0.72). The effect estimate between lag2–3 $PNC_{<100}$ and CVM was positive during the warmer season (April–September, 2.30%; 95% CI: $-1.28, 6.06$) but negative during colder months (October–March, -2.07% ; 95% CI: $-5.44, 1.43$; interaction $p=0.08$).

Discussion

Our findings suggest that short-term exposures to lung-deposited PSC and PNC in the ultrafine (electric mobility diameter <100 nm) and fine (100–750 nm) particle size ranges (especially PNC 50–500 nm), are associated with small increases in daily NM and CVM. Associations suggested immediate (lag0–1) and slightly delayed (lag4–7) effects, and effect estimates were more precise for all NM than for the smaller subset of deaths due to cardiovascular disease. Associations of size-specific PNC were mostly robust to the adjustment for PM_{10} and O_3 , and slightly changed when adjusted for NO_2 . Effect estimates for $PNC_{100-750}$ and PSC were similar to those observed for PM_{10} , suggesting immediate as well as delayed effects on NM and CVM. Based on an IQR increase in respective exposure concentration, positive associations for PNC in the 50–500 nm range were stronger than positive associations for PM_{10} .

In this study, we were able to investigate size-dependent PNC, including three size fractions in the UFP size range (13.3–30, 30–50, 50–500 nm) and three size fractions in the fine range (100–250, 250–500, 500–750 nm), aiming to identify the most pathogenic size fraction. We observed that the PNC of the smallest size ranges (13.5–50 nm) was inversely associated with natural and cause-specific mortality. This immediate inverse association of UFPs with natural and cause-specific mortality has been observed before in a German time-series study, showing inverse associations at lag1 and lag2, mainly driven by the smallest particle size, yet less pronounced than shown in our results (Stölzel et al. 2007). In contrast to the inverse association

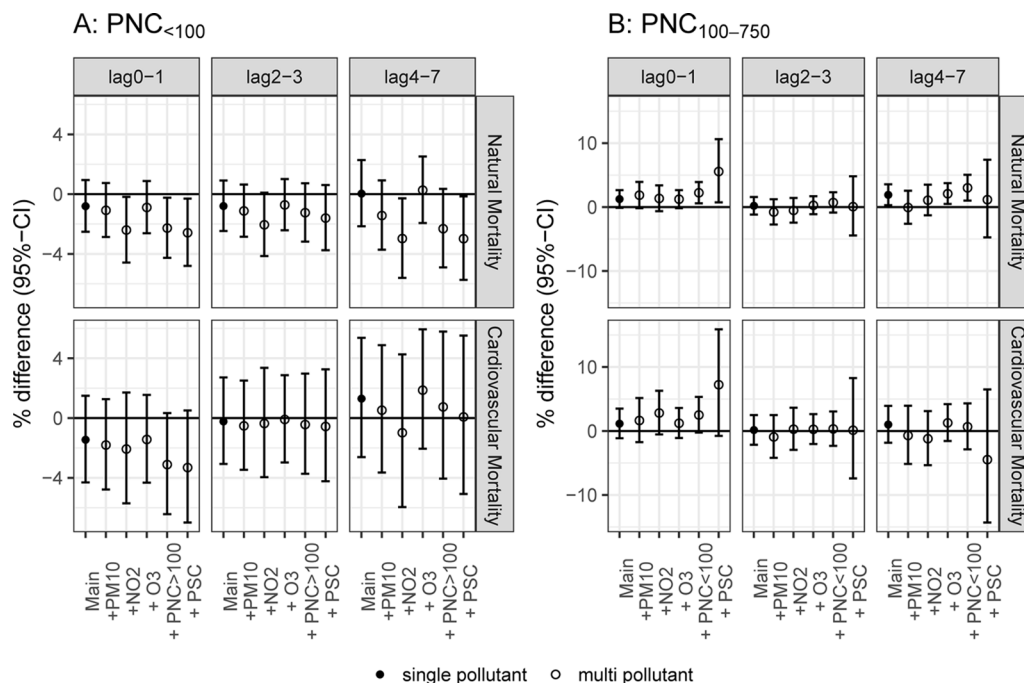


Figure 4. Effect estimates for percentage differences (95% confidence interval) [% (95% CI)] in natural and cardiovascular-specific mortality in the Ruhr Area between March 2009 and December 2014 per IQR increase in (A) ultrafine particles ($PNC_{<100}$) and (B) fine particles ($PNC_{100-750}$, short: $PNC_{>100}$) for averaged lags (lag0–1, lag2–3, lag4–7), estimated in Poisson regression models, adjusted for time trend, temperature, humidity, day of week, holidays, period of seasonal population decrease, and influenza with additional adjustment for PM_{10} , NO_2 , O_3 , $PNC_{>100}$ ($PNC_{<100}$), and PSC. Note: IQR, interquartile range; NO_2 , nitrogen dioxide; O_3 , ozone; PM_{10} , particulate matter $\leq 10 \mu m$ in aerodynamic diameter; $PNC_{<100}$, size-specific particle number concentration of particles $<100 nm$ electrical mobility diameter; $PNC_{100-750}$, PNC of particles with 100–750 nm electrical mobility diameter; PSC, particle surface area concentration.

of the smallest size fraction, we observed positive immediate and delayed associations between UFP with an electric mobility diameter of 50–100 nm and daily mortality, which were similar to associations of other fine particle metrics ($PNC_{100-750}$, PSC, and PM_{10}). Among the fine to submicrometer particle size fractions ($PNC_{100-750}$), particles with an electric mobility diameter from 100 to 250 and 250 to 500 nm revealed the clearest health effect estimates. Moreover, and in contrast to the inverse immediate associations, UFPs indicated delayed associations with CVM, as has been reported by others (Lanzinger et al. 2016; Stafoggia et al. 2017).

Typically, specific size ranges are related to major emission sources. Particles in the nucleation mode ($<30 nm$) reflect mainly new particles formed by gas-to-particle conversion, including particles originating from gaseous precursors in vehicle exhaust such as NO_2 (Vu et al. 2015). Particles in the Aitken (30–100 nm) and accumulation (100 nm–1 μm) mode with an electric mobility diameter of 30–500 nm contain soot particles from combustion processes, including coal burning power plants, oil combustion, and combustion-engine powered vehicles (Vu et al. 2015). The modal size of vehicle-generated soot particles is in the size range of 100–250 nm (Harrison et al. 2010). Moreover, the particle size fraction 50–250 nm contains diesel exhaust particles, which have been shown to be specifically pathogenic in experimental settings (Mills et al. 2007). Particles from gasoline-powered engines, on the other hand, are typically smaller than diesel soot and mainly form particles $<80 nm$ (Vu et al. 2015). Particles from mechanical abrasion processes such as brake, tire, and road wear are larger and can be found in the accumulation and coarse ($>1 \mu m$) mode (Vu et al. 2015). Moreover, accumulation mode particles encompass mostly long-range transported aerosols, whereas nucleation and Aitken mode particles usually have short lifetimes. From a biologic point of view, particles below 50 nm have the highest deposition efficiency, whereas

Aitken and specifically accumulation mode particles deposit less efficiently (Kreyling et al. 2006). Moreover, particles below 50 nm contain a higher amount of soluble constituents.

Based on our findings, which show the largest associations for particles sized 50–500 nm, we concluded that primary combustion-generated soot particles might be more harmful than secondary particles formed via nucleation and condensation. This poses the question of whether the PNC in the size range from 50 to 500 nm might actually be a more important metric than the commonly used UFPs, which are defined as particles with a diameter $<100 nm$.

The repeatedly observed inverse associations for UFP ($PNC_{<100}$) in temperature- and humidity-adjusted models seemed to be driven by the smallest particle size fraction (13.5–30 nm) and remained striking. From a biologic point of view, it seems implausible that the particles contained in the nucleation mode have a true protective effect on mortality. Associations with $PNC_{<100}$ at lag0–1 remained inverse when additionally adjusted for NO_2 and O_3 in separate models, and they could not be explained through any investigated effect modification. In fact, point estimates became even more negative when O_3 was below the 75th percentile.

Most time-series studies on short-term mortality effects of UFPs today have conducted single pollutant analyses. The important question remains, whether the observed effects of ultrafine or any other specific particle size fraction act independently of other pollutants considering that they are sharing potential sources. The answer to this question is of great interest with regard to the regulation of exposure and prevention of adverse health effects. In our study, inverse associations between UFP and natural and cause-specific mortality were robust to adjustment for O_3 or PM_{10} , but tended to move further from the null (i.e., became more negative) with adjustment for NO_2 , $PNC_{100-750}$, or PSC. Similar patterns of for UFP-associations have been observed after adjustment for NO_2 , and also for $PM_{2.5}$ before (Stafoggia et al. 2017), whereas

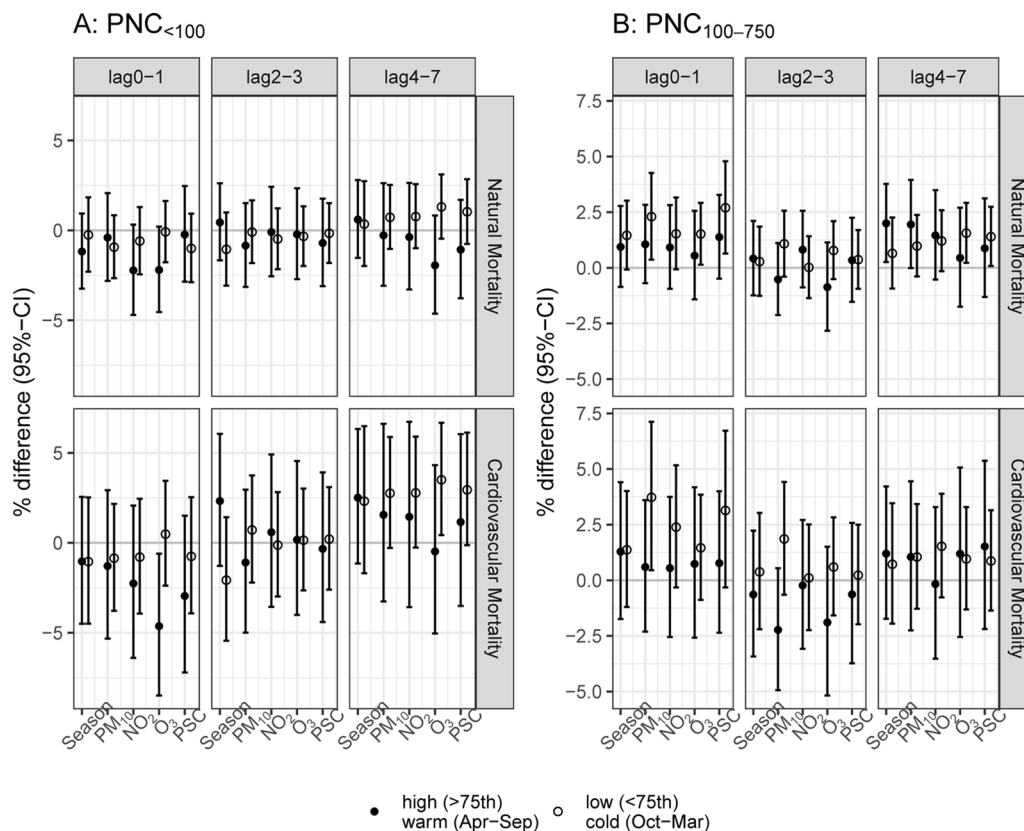


Figure 5. Estimated effect modification by season and copollutants for short-term (lag0–1, lag2–3, lag4–7) percentage differences in natural and cardiovascular mortality based on an IQR increase in the ultrafine particle concentration ($PNC_{<100}$) in the Ruhr Area between March 2009 and December 2014 using Poisson regression models, adjusted for time trend, temperature, humidity, day of week, holidays, period of seasonal population decrease, and influenza. (Corresponding numeric data are provided in Table S3.) Note: IQR, interquartile range; $PNC_{<100}$, size-specific particle number concentration of particles <100 nm electrical mobility diameter; $PNC_{100-750}$, PNC of particles with an electrical mobility diameter between 100 and 750 nm.

others reported associations between prolonged exposure to UFP independent of particle mass exposures (Lanzinger et al. 2016). These contrary findings probably reflect important differences across studies caused by the different mixture of particles and sources due to the region of interest.

The rarely investigated lung-deposited PSC showed similar results as $PNC_{100-750}$ or PM_{10} , namely immediate and delayed associations with NM and CVM. Moreover, PSC correlated highly (>0.7) with PNC of particles sized 50–500 nm, which were the size-classes revealing the most clearly observed (immediate and delayed) health effect estimates.

Despite a strong correlation between $PNC_{100-750}$, PM_{10} and PSC, PSC constitutes an integrated measure of reactive particle surface and deposition efficiency, which serve as a better marker understanding effect mechanisms between the inhalation of particles and health outcomes than solely mass-based or number-based metrics. It has been discussed that particle area surface plays a greater role in oxidative stress and pro-inflammatory effects than particle mass or particle number because the surface is the relevant location for oxidative processes (Hussain et al. 2009). Within this study, however, we were not able to disentangle biological effects of the mass, the number, and the surface of particles.

Season did not affect effect estimates of UFPs in the Ruhr Area consistently in terms of lag-time and cause of mortality, although season clearly affected effect estimates of UFPs on natural and cause-specific mortality and hospital admissions in other European regions (Samoli et al. 2016; Stafoggia et al. 2017). However, in comparison with the Mediterranean climate, the Ruhr Area has a more temperate climate with cool summers and

mild and rainy winters, not displaying the strong seasonal pattern observed in Italy or Greece. Overall, we did not observe a consistent pattern among selected effect modifiers regarding associations between fine or ultrafine PNCs and natural or CV mortality.

Overall, our results are in line with results of other time-series studies, showing immediate (lag 0–1) and delayed effects (\geq lag 4) of fine particles, while observing more delayed effects of UFPs on natural and cause-specific mortality (Breitner et al. 2009; Ibaldo-Mulli et al. 2002; Lanzinger et al. 2016; Stafoggia et al. 2017; Stölzel et al. 2007; Wichmann and Peters 2000). One of the first studies on UFPs reported the largest associations between UFPs and nonaccidental mortality for delayed (lag4) exposures in Erfurt, Germany (Wichmann et al. 2000). These results were confirmed in a reanalysis of an extended data base (Breitner et al. 2009; Stölzel et al. 2007). A European study including five cities (Augsburg, Chernovtsy, Dresden, Ljubljana, and Prague) reported an increase in respiratory mortality after 6 d (lag0–5) (Lanzinger et al. 2016). Another European study including eight cities (Helsinki, Stockholm, Copenhagen, Ruhr Area, Augsburg, Rome, Barcelona, and Athens) observed weak delayed associations (lag5–7) with NM and cardiovascular and respiratory mortality (Stafoggia et al. 2017). In contrast, several large multicenter time-series studies on fine particle mass showed primarily immediate effects on daily mortality (HEI 2010; Katsouyanni and Samet 2009; Samoli et al. 2008). Possible biological explanations for these different temporal patterns between size-specific particles could be local inflammation induced by fine particles in the bronchi and lung tissue, which may lead to immediate effects on mortality. In contrast, smaller particles such as UFPs may partly escape pulmonary clearing mechanisms, translocate across biologic

membranes, and gain access to the vasculature and systemic circulation, stimulating systemic inflammatory mechanisms. This process can lead to an increased risk for cardiovascular events after several days. The overall reported delayed associations of UFPs and cardiovascular health seem plausible from this biological perspective. Supporting our findings, Stölzel et al. (2007) reported slightly higher delayed effect estimates with CVM than with NM for the UFPs.

Several limitations should be acknowledged in our study. The most obvious one is the small number of mortality events, limiting the statistical power of our results, especially regarding cause-specific mortality. Moreover, we have fitted several models to estimate adverse health effects of multiple pollutants regarding multiple lags and time windows, yielding a higher possibility of rejecting a null effect. However, in this study we aimed to identify a temporal pattern of different sized particles on the different causes of death instead of focusing on associations of single-day lags. In addition, this study used only one monitor as the reference exposure for three adjacent cities. Although PM₁₀ and PM_{2.5} tend to be more homogeneously distributed over wider spatial regions with daily changes primarily dependent on meteorology, daily UFP concentration changes might differ considerably depending on location and local sources, especially in proximity to major roads or highways (Cyrus et al. 2008; Pekkanen and Kulmala 2004). For our study we assumed that the central monitor, placed at an urban background station, properly captured the day-to-day variability relevant for the surrounding population, as was assumed by others as well (Cyrus et al. 2008). Moreover, the high correlation of several exposure metrics limited our power to disentangle individual metric effects. Another limitation includes the lack of daily measurements of PM_{2.5}, which has been shown to confound health effects of UFPs (Stafoggia et al. 2017).

The main strength of this study is the consistent exposure assessment throughout the study period of approximately 6 y. Furthermore, the study benefits from an in-depth characterization of particles, with the aim to specifically capture toxicologically important particle characteristics, including size-specific PNC and total lung-deposited PSC, a metric that has rarely been investigated in epidemiological studies to date. Moreover, the measurement site was located next to a routine monitoring site, enabling us to make use of monitored copollutants such as PM₁₀, NO₂, or O₃, which can potentially confound or modify UFP effects on health.

Conclusions

Size-specific PNC (50–500 nm) and lung-deposited PSC indicated an association with NM and CVM in the Ruhr Area, showing immediate (lag0–1) and delayed (lag4–7) effect estimates revealing slightly higher point estimates than those of PM₁₀ based on an IQR increase of exposure concentration. Although results from PM, PNC, and PSC could not be disentangled, it might be beneficial to investigate particle number size distributions, which can be linked to emission sources, in addition to the particle mixture captured by the measurement of PM₁₀ only. Moreover, PSC could be used as an alternative metric that integrates particle size distribution as well as deposition efficiency. Further investigations are needed to establish the different temporal patterns among different particles sizes and surfaces.

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